The effect of low volume sprint interval training in patients with non-alcoholic fatty liver disease

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ABSTRACT

Objectives: Exercise is an important part of disease management in patients with non-alcoholic fatty liver disease (NAFLD), but adherence to current exercise recommendations is poor. Novel low-volume sprint interval training (SIT) protocols with total training time commitments of ≤30 min per week have been shown to improve cardiometabolic risk and functional capacity in healthy sedentary participants, but the efficacy of such protocols in the management of NAFLD remains unknown. The aim of the present study was to examine whether a low-volume SIT protocol can be used to improve liver function, insulin resistance, body composition, physical fitness, cognitive function and general well-being in patients with NAFLD.

Methods: In the present study, 7 men and 2 women with NAFLD (age: 45±8 y, BMI: 28.7±4.1 $kg \cdot m^{-2}$) completed a 6-week control period followed by 6 weeks of twice-weekly SIT sessions (5-10×6-s 'all-out' cycle sprints). Body composition, blood pressure, liver function, metabolic function, functional capacity, cognitive function and quality of life were assessed at baseline, following the control period, and following the SIT intervention.

Results: Walking speed during the walk test (+12%), estimated $\dot{V}O_2max$ (+8%), verbal fluency (+44%), and blood platelet count (+12%; all $p<0.05$) significantly increased during the control period. These measures remained significantly raised compared to baseline following the SIT intervention, but did not significantly change any further compared to the post-control time-point. Diastolic blood pressure decreased from 87±10 to 77±8 mm Hg from the end of the control period to the end of the SIT intervention ($p<0.05$).

Conclusion: This study does not support the use of 6 weeks of a low volume SIT protocol involving twice-weekly sessions with 5-10×6-s 'all-out' cycle sprints as an intervention for NAFLD disease management.

Keywords:

SIT; all-out; NAFLD; NASH; liver function; physical function

Abbreviations:

ALT: alanine aminotransferase; ANOVA: analysis of variance; AST: aspartate aminotransferase; AUC: area under the curve; BMI: body mass index; EPO: end power output; FIB-4: fibrosis-4 score; HIIT: high-intensity interval training; HOMA-IR: homeostasis model assessment of insulin resistance; IR: insulin resistance; MICT: moderate-intensity continuous training; MPO: mean power output; MS: metabolic syndrome; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis;

PPO: peak power output; OGTT: oral glucose tolerance test; SIT: sprint interval training; T2D: type 2 diabetes; $\dot{V}O_2$max: maximal aerobic capacity.

1 INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is among the most common causes of chronic liver disease, and its prevalence is increasing globally [1]. In the Western world NAFLD tends to be associated with obesity, hyperlipidaemia and insulin resistance (IR) [2]. As such it is considered to represent the hepatic aspect of the metabolic syndrome (MS) [3, 4], and is associated with an increased risk for the development of cardiovascular disease and type 2 diabetes [2]. It is now accepted that IR is a key aspect in the pathophysiology of both MS and NAFLD, and that IR should be addressed in clinical treatment of patients with NAFLD [2]. Untreated, in a subset of patients NAFLD may progress to non-alcoholic steatohepatitis (NASH) with possible subsequent cirrhosis, liver failure or hepatocellular carcinoma [3, 5], and it is an increasingly frequent reason for liver transplantation [6]. Furthermore, NAFLD is associated with increased risk of dying from cardiovascular disease or cancer [7].

Lifestyle changes such as weight loss and exercise are fundamental aspects of NAFLD management, as they have been shown to reduce insulin resistance, steatosis and liver fat, and improve liver function [4, 8, 9, 10, 11, 12]. Both aerobic and resistance exercise result in improvements in liver fat levels in patients with NAFLD and type 2 diabetes (T2D) [13]. Aerobic exercise has been shown to improve liver steatosis independently of weight loss [14]. A systematic review by Keating et al. [15] concluded that exercise was beneficial in NAFLD, despite evidence being drawn from small studies with a wide variation in exercise prescription. A retrospective study of 813 patients with NAFLD, diagnosed by liver biopsy, suggested that vigorous exercise more effectively reduced the risk of NAFLD and liver fibrosis compared to moderate exercise, though this was based on self-reported data on exercise quantity and intensity [16]. Conversely, a recent randomised controlled trial concluded that low- and high-intensity aerobic exercise were equally effective at reducing intrahepatic lipid in inactive overweight/obese adults [17]. To date, no conclusions have been reached on the optimum quantity and intensity of exercise required to treat NAFLD [1, 18, 19].

Despite the known positive effects of exercise, patients with NAFLD are often more sedentary than unaffected individuals, and few patients achieve the recommended daily and weekly guidelines for physical activity [6]. As lack of time is a common perceived barrier to exercise, time-efficient alternatives to aerobic exercise have been proposed, including (sub)maximal high-intensity interval training (HIIT) and supramaximal sprint interval training (SIT) [20].

The ‘classic’ SIT protocol was developed a decade ago and consists of 4-6 repeated 30-s Wingate sprints [21]. This protocol was shown to be associated with aerobic adaptations similar to substantially higher volumes of moderate-intensity continuous training (MICT) [21, 22]. We subsequently demonstrated rapid improvements in measures of insulin sensitivity and glycaemic control in healthy volunteers following two weeks of SIT [23]. However, this SIT protocol is extremely demanding and raises concerns over compliance, health and safety, particularly in those with existing disease [20, 24]. Furthermore, the classic SIT protocol is not as time-efficient as often proposed, as the need for recovery periods in between sprints means that the total time-commitment per training session is close to 30 min, similar to recommendations for MICT [25].

To address these issues, in recent years studies have investigated whether the classic SIT protocol can be made shorter and less strenuous, while retaining the associated health benefits [26, 27, 28, 29, 30, 31]. There is now clear evidence that substantially reducing the total time exercising at high intensity does not attenuate important adaptations such as improvement in maximal aerobic capacity ($\dot{V}O_2max$) [32]. In recent studies we have shown that a SIT protocol using repeated efforts as brief as 6 seconds is associated with improvements in health and physical function in middle-aged [33] and elderly adults [34], as well as in trained athletes [35]. This SIT protocols may provide a suitable alternative to MICT for primary prevention in sedentary individuals [25], but it could also have potential as a treatment for noncommunicable diseases including type 2 diabetes [36], metabolic syndrome, and NAFLD. No previous studies have investigated the efficacy of repeated brief supramaximal sprints for improving health markers in patients with NAFLD. Thus, the aim of the present study was to examine whether a low volume SIT protocol results in improvements in liver function, insulin resistance, body composition, physical fitness, cognitive function and general well-being in patients with NAFLD.

2 MATERIAL AND METHODS

2.1 Participants

Ten men and 2 women diagnosed with NAFLD with steatosis (n=7) or NASH (n=5) were recruited from liver clinics in Ninewells Hospital, Dundee. Three male participants subsequently withdrew due to medical problems unrelated to the study (2 prior to and 1 during the training intervention), leaving 9 participants who completed the study (age: 45±8 y, BMI: 28.7±4.1 $kg \cdot m^{-2}$; 5 Caucasian, 2 South-East Asian, 2 South Asian). The diagnosis was confirmed by a hepatologist on clinical grounds, including blood test screening and hepatic ultrasound scan, without necessarily requiring confirmation by liver biopsy. Those aged below 20 y or above 59 y were excluded, as were those with uncontrolled hypertension, unstable cardiovascular, pulmonary or metabolic disease, and those with significant mobility problems. Participants were screened for suitability through a Physical Activity Readiness Questionnaire for Everyone (PAR-Q+). The study used a single-group repeated measures design, with each participant undergoing an initial 6-week control period, followed by a 6-week intervention (i.e. each participant acted as their own control). All participants gave written informed consent. Ethics approval was obtained from Scotland A Research Ethics Committee (REC reference: 15/SS/0108), and the study complied with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (ID: NCT02528305).

2.2 Experimental Procedures

Participants attended for baseline assessment having fasted from midnight the day before. Height was measured (Seca stadiometer, Seca, Hamburg, Germany) followed by body mass and body composition (segmental bioimpedance analyser, Tanita MC-780MA, Tanita, Japan). Ankle-brachial pressure index (ABPI) was recorded supine (watch BP office ABI TWIN200ABI, Microlife Watch BP, AG Switzerland) before a venous blood sample was taken. One lithium-heparin tube was centrifuged (Eppendorf Centrifuge 5804R, Hamburg, Germany) at 1600 rpm for 8 min, after which serum was separated and refrigerated to prevent insulin degradation. Samples were transferred to an accredited hospital laboratory (Clinical Pathology Accreditation (UK) Ltd) for analysis of fasting glucose, insulin, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelets by standard procedures. Homeostasis model assessment of insulin resistance (HOMA-IR [37]) and FIB-4 (fibrosis-4 score, a non-invasive marker of fibrosis [38]) were calculated. Finger-prick blood samples were taken for measurement of plasma glucose (Freestyle freedom-lite Glucometer, Abbott Diabetes Care, Maidenhead, UK) prior to and 20, 40, 60, 80, 100 and 120 min following consumption of 75 g glucose (410 mL Lucozade Original, GlaxoSmithKline, Brentford, UK)) for an oral glucose tolerance test

(OGTT). The response to glucose was assessed from calculating the area under the curve (AUC) using the trapezoid rule. Immediately following Lucozade ingestion, the participants completed the 36-Item Short Form Health Survey (SF-36) to assess general well-being [39]. Thirty min after the glucose load, episodic memory was assessed by immediate recall of 10 words, with delayed recall to test semantic memory 10 min later. Additionally, verbal fluency was used to assess executive function, via the listing of words starting with a particular letter of the alphabet. After completion of the OGTT, physical function was assessed by a 'get up and go' test (GUAG) [40], where the participants were timed while standing up from a chair unaided, with arms crossed, walking 3 m, turning round, returning to the chair and sitting down again, all as quickly as possible. This was performed 3 times, with the mean time taken. Finally, physical fitness was assessed by estimating $\dot{V}O_2$max from a submaximal walking test [41]. The participants wore a heart rate monitor (Polar T31 HR monitor, Polar Electro, Warwick, UK) and walked for 4 min on a treadmill with a flat gradient (Mercury H/P/Cosmos, Nussdorf-Traunstein, Germany) without any encouragement. They were allowed to adjust the treadmill speed during this time. Thereafter, the gradient was increased to 5%, during which time the speed was fixed. After 4 min of walking at a 5% gradient, participants were asked to rate their perceived exertion (RPE) using the Borg Scale [42], and their heart rate (HR) and walking speed were recorded in order to estimate their $\dot{V}O_2$max using the equation by Ebbeling et al. [41]. Walking speed was also divided by RPE to gauge effort relative to speed, to determine whether participants could walk faster following SIT but perceive similar effort required to that in baseline testing.

2.3 Second Assessment

In order to allow the participants to make any changes to their diet and lifestyle as advised by their hepatologist without affecting the study, the baseline assessment was repeated at the same time of day, six weeks after the initial assessment. This allowed the participants to act as their own controls. Thereafter, the participants started the SIT intervention.

2.4 Training Intervention

Participants had their blood pressure checked prior to each training session (Boso-medicus, Bosch & Sohn, Jungingen, Germany). The training comprised twice-weekly supervised SIT sessions on Monark Peak Bikes (Ergomedic 894E, Monark Exercise AG, Vansbro, Sweden), with heart rate (Polar, Oulu, Finland) recorded during each session. After a 2-min unloaded warm-up at a cadence of 50 rpm, participants were asked to sprint at maximum effort for 6 s against a resistance equivalent to 7% of body mass for men and 6% of body mass for women, which was applied automatically when reaching 100 rpm. This was followed by 1 min of passive recovery, or until heart rate dropped below 120

beats·min^{-1}. Sprints were repeated 5 times in sessions 1-3 and 6 times in session 4, after which an additional sprint was added each week (e.g. 10 sprints in week 6; minimum session duration of 13 min). Peak (PPO), mean (MPO), and end power output (EPO) were recorded.

2.5 Third Assessment

The baseline assessment was repeated as previously detailed, 5±1 days after the last training session.

2.6 Statistical Analysis

All data shown are means±SD. Statistical analysis was performed using SPSS statistical software (v21). All parameters were analysed for differences between the 3 time-points (baseline / post control / post SIT) using repeated measures ANOVA, with *post hoc* analysis with Bonferroni correction in the case of significant main effects. Paired sample t-tests were used to analyse differences between the first and last training session for mean heart, PPO, MPO and EPO. Significance was accepted at $p<0.05$.

3 RESULTS

The nine participants who completed the study performed all 12 SIT sessions (100% adherence). PPO, MPO and EPO produced in the first 5 sprints were significantly higher in the last compared to the first SIT sessions (**Figure 1**; $p<0.001$). Results for the body composition measures, blood pressure, blood measures, functional tests, memory tests and the SF-36 are shown in **Table 1**. Walking speed during the 12-min walk test (+12%), estimated $\dot{V}O_2max$ (+8%), verbal fluency (+44%), and blood platelet count (+12%; all $p<0.05$) significantly increased during the control period. These measures remained significantly raised compared to baseline following the SIT intervention, but did not significantly change any further compared to the post-control time-point. Diastolic blood pressure decreased from 87 ± 10 to 77 ± 8 mm Hg from the end of the control period to the end of the SIT intervention ($p<0.05$). No other significant changes were observed, including in the 8 subcomponents that make up the total score for the SF-36 questionnaire (physical function, role physical, general health, mental health, social functioning, vitality, bodily pain, role emotional; data not shown).

4 DISCUSSION

The aim of the present study was to examine the health benefits of a low volume SIT protocol in patients with NAFLD. The supramaximal exercise sessions were well-tolerated by the participants, but the data do not support the use of this 5-10 × 6-s 'all-out' SIT protocol in the management of liver disease: although diastolic blood pressure significantly improved following 6 weeks of training, no other parameters were affected.

This study was the first to examine the efficacy of supramaximal SIT in patients with NAFLD. Previous research justifies investigations into the efficacy of interventions utilising high exercise intensities. For example, in a recent review article Keating et al. [43] stated that higher exercise intensities may lead to superior adaptations. A study by Oh et al. [44], looking at the therapeutic effects of aerobic high-intensity interval training, resistance training, and moderate-intensity continuous aerobic training in patients with NAFLD, demonstrated that each of these modalities was effective at reducing hepatic fat content, but that only aerobic high-intensity interval training was effective at improving hepatic stiffness. Recently, a submaximal HIIT protocol was used by Hallsworth et al. [45] in patients with NAFLD, and this protocol was shown to be effective at improving liver fat, body composition, and cardiac function following 12 weeks of training. However, the 3 weekly sessions took 30-40 min to complete, and included 5 repetitions of 2-3 min of cycling at an RPE of 16-17 (equivalent to 'very hard'). It remains to be seen whether the uptake of, and adherence to, such a strenuous intervention is sufficient to warrant its use as an alternative to current physical activity recommendations involving lower-intensity, less strenuous MICT of a similar duration. The benefit of low volume SIT protocols is that health benefits can be achieved within a minimal total time commitment (≤30 min per week) and with acceptable ratings of perceived exertion [25]. However, the minimum effective SIT volume remains unknown. The present study suggests that performing 5-10 × 6-s 'all-out' cycle sprints twice a week is sufficient to lower diastolic blood pressure. This is important as even small decreases in blood pressure can result in substantial reductions in cardiovascular disease [46, 47], with measurable effects down to at least 115 mm Hg systolic blood pressure and 75 mm Hg diastolic blood pressure [48]. However, the lack of improvements in functional capacity, estimated $\dot{V}O_2$max, liver function, measures of glycaemic control, body composition, cognitive function, and quality of life, suggests that the present training volume was insufficient to support the use of this SIT protocol in disease management of patients with NAFLD.

In previous studies with an identical SIT protocol we demonstrated significant improvements in performance in athletes [35], and in health and physical function in middle-aged [33] and elderly adults [34]. Similarly, we have shown improvements in health markers in sedentary young adults using a protocol with longer (20 s) but fewer (2) sprints [29, 30], involving a comparable total time exercising at high-intensity. Therefore, it is unclear why the participants in the present study did not present with similar adaptations. A potential explanation is that individuals with metabolic disorders may have an impaired response to training. Indeed, impaired responses to aerobic exercise have been reported in patients with T2D or metabolic syndrome [49, 50], and patients with T2D appear to respond less well to low volume SIT [36] compared to sedentary but healthy individuals [29, 30]. Furthermore, longer T2D disease duration is associated with poorer improvements in insulin sensitivity and glycaemic control following aerobic exercise training [51]. Conversely, other studies have reported greater benefits of exercise in people with poorer baseline insulin sensitivity [52]. Although various types of medication, including metformin and statins, have been shown to attenuate exercise-induced adaptations [53, 54, 55], only one participant in the present study was taking statins, and none were on anti-diabetic medication. Future research should answer the question whether patients with metabolic disorders can be expected to respond to different exercise training protocols in a similar way to healthy individuals, but the present study indicates that 6 weeks of training involving 2 sessions and a total of 60-120 s of 'all-out' cycling exercise per week is insufficient to improve a range of health markers.

It is unclear what caused the significant improvements in walking speed during the 12-min walk test, estimated $\dot{V}O_2$max, verbal fluency, and blood platelet count following the 6-week control period. We did not perform familiarisation tests prior to the baseline testing session, and we do not have data on potential changes in diet or physical activity levels during the control period that could explain these findings. Therefore, future studies would benefit from a randomised controlled study design with parallel arms, and measurement of potential changes in diet and physical activity levels.

In conclusion, this study does not support that performing 6 weeks of a low volume SIT protocol involving twice-weekly sessions with 5-10 × 6-s 'all-out' cycle sprints is an effective intervention for NAFLD disease management.

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Authors' Contributions

CM, JB and NV conceived of the study and participated in its design. CM, JD and JB participated in participant recruitment and data collection. CM and NV performed data analysis and drafted the manuscript. JD and JB provided feedback on the final manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Conflicts of interest

The authors report no conflicts of interest

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Table 1: Changes in parameters following the 6-week control phase and the 6-week SIT intervention

	Baseline	Post control	Post SIT
Body composition:			
Body mass (kg)	85.2±18.6	85.9±19.6	86.0±20.2
BMI ($kg \cdot m^{-2}$)	28.7±4.1	28.9±4.5	29.0±4.8
Body fat (%)	30±8	29±8	28±7
Trunk fat (%)	27±6	29±5	29±6
Blood pressure:			
Diastolic pressure (mm Hg)	85±13	87±10	77±8 c
Systolic pressure (mm Hg)	139±18	142±13	135±20
Mean arterial pressure (mm Hg)	103±13	105±10	96±11
Ankle-brachial pressure index	1.15±0.16	1.08±0.18	1.13±0.27
Blood measures:			
Plasma glucose ($mmol \cdot L^{-1}$)	5.5±0.6	5.4±0.6	5.6±0.6
Plasma insulin ($mU \cdot L^{-1}$)	27±15	37±35	27±14
HOMA-IR	6.9±4.7	9.6±10.6	7.0±4.3
Plasma glucose AUC OGTT (units)	981±136	1030±182	1010±247
Plasma triglycerides ($mmol \cdot L^{-1}$)	1.83±0.91	1.73±1.03	1.76±0.51
Platelets ($x10^{9} \cdot L^{-1}$)	252±56	276±66 b	280±66 a
ALT ($U \cdot L^{-1}$)	65±20	71±23	61±17
AST ($U \cdot L^{-1}$)	30±7	30±7	28±4
AST/ALT	0.51±0.17	0.47±0.20	0.50±0.21
FIB-4	0.68±0.18	0.60±0.19	0.60±0.18
Functional tests:			
Get up and go (s)	6.5±0.7	6.2±0.6	5.9±0.6
12-min walk speed ($km \cdot h^{-1}$)	4.2±0.7	4.7±0.9 a	4.8±0.8 a
12-min walk HR ($beats \cdot min^{-1}$)	116±18	116±22	116±10
12-min walk RPE	12.1±2.1	12.3±1.0	11.2±1.9
12-min walk RPE/speed	3.0±0.9	2.7±0.7	2.5±1.0
12-min walk estimated $\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.9±6.5	37.6±7.2 a	38.5±7.2 a
Memory test:			
10-word immediate recall	6.0±1.6	6.9±1.3	6.3±1.5
10-word delayed recall	4.4±1.2	5.1±1.8	4.6±1.7
Verbal fluency	8.1±3.6	11.7±4.4 a	11.1±2.9 a
Quality of life:			
SF-36 total score (%)	71.1±16.3	72.0±19.9	79.7±16.7

Values shown are means±SD. Significant difference from baseline: a ($p<0.05$), b ($p<0.01$); significant difference from post control: c ($p<0.05$)

Figure 1 Power output during the first 5 sprints of the first and last training sessions. Each line shows peak (PPO), mean (MPO), and end (EPO) power output. PPO, MPO, and EPO were significantly higher during the last session compared to the first session.